REMARKS

In accordance with the present invention, there is provided three-dimensional structural information related to farnesoid X receptor (FXR) molecules. In a particular aspect, there are provided compositions comprising an exemplary ligand binding domain of FXR molecules in crystalline form (as described, for example, by structure coordinates obtained by X-ray crystallography), and computers utilizing such structure coordinates to provide information regarding the ligand binding domain of FXR molecules and ligands therefor. In another aspect, the invention provides methods of utilizing such structure coordinates for screening compounds to identify those which are capable of binding FXR molecules, and those which are agonists, partial agonists and antagonists of FXR molecules.

By the present communication, paragraph **[0032]** has been amended to explicitly identify the amino acid residues referred to in Appendix 1 as being residues 248-270 and 286-475 of SEQ ID NO:1. Upon such entry, the application is submitted to be in full compliance with the requirements for a sequence listing.

In addition, by the present communication, claims 14, 18, 19 and 31 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. In addition, by the present communication, claims 1-3, 6-13, 15, 20-23, 32 and 33 have been cancelled without prejudice, subject to Applicants' right to pursue the subject matter thereof in one or more applications which claim priority from the present application.

The amendments provided herewith are submitted to place this application in condition for allowance, or, at a minimum, in better condition for appeal. In addition, the amendments provided herewith substantially reduce the number of claims under consideration (i.e., 20 pending claims have been reduced to only 4). Accordingly, entry of the amendments provided herewith is submitted to be proper. Entry, therefore, is respectfully requested.

Upon entry of the amendments submitted herewith, claims 14, 18, 19 and 31 will remain pending in the application, with claims 14, 18 and 19 under active prosecution, and claim 31 withdrawn from consideration, subject to a request for rejoinder thereof. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination, is presented in the Listing of Claims, beginning on page 3 of this communication, with an appropriate status identifier for each claim.

Claim Objections

The objections to claims 14, 15 and 18 for alleged informalities therein are respectfully traversed, and have been rendered moot by the amendments submitted herewith, whereby the claim has been cancelled (with reference to claim 15) or all reference to "plurality of" structure coordinates has been deleted (with reference to claims 14 and 18). Accordingly, reconsideration and withdrawal of the objection to these claims are respectfully requested as the objections do not apply to the present claims.

Compliance with Sequence Rules

The assertion that the present application allegedly fails to fully comply with the requirements of 37 C.F.R 1.821 through 1.825 (see page 3 of the Office Action) is acknowledged, and has been rendered moot by the amendments submitted herewith, whereby reference to Appendix 1 in the specification has been amended to explicitly identify the amino acid sequence disclosed within the atomic coordinates set forth in Appendix 1 as comprising residues 248-270 and 286-475 of SEQ ID NO:1.

Rejections under 35 U.S.C. § 112

Written description

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement, is once again respectfully traversed for at least the reasons of record.

As a preliminary matter, this rejection has been rendered moot with respect to claims 15 and 20 by the cancellation of these claims.

With respect to the remaining claims (i.e., claims 14, 18 and 19), Applicants once again respectfully disagree with the Examiner's assertion that the disclosed invention allegedly contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Office Action, p. 4, ll. 9-12).

Contrary to the Examiner's assertion, it is respectfully submitted that the specification provides substantial information to convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the invention as claimed herein.

Claim 14, as amended herein, and claims 15 and 18 dependent therefrom, are directed to methods of screening molecules to determine those which are capable of binding to a farnesoid X receptor (FXR) molecule. The claimed methods require:

> modeling a test molecule that potentially interacts with a ligand binding domain of a farnesoid X receptor (FXR) comprising amino acid residues 248 – 476 of SEQ ID NO:1,
>
> wherein said ligand binding domain is further defined by the structure coordinates set forth in Appendix 1, or a portion thereof sufficient to define the points of interaction between said ligand binding domain and a ligand therefor, and
>
> determining whether there is repulsive electrostatic interaction between said test molecule and said FXR molecule,
>
> whereby those test molecules which lack repulsive electrostatic interaction with said FXR molecule in their bound state are capable of binding to a farnesoid X receptor (FXR) molecule.

Thus, the invention methods require modeling a test molecule with a defined ligand binding domain of a farnesoid X receptor, then determining if the test compound is capable of binding to

a farnesoid X receptor based on the lack of repulsive electrostatic interaction with FXR molecule in their bound state.

Similarly, claim 19, as amended herein, further defines Applicants' invention by requiring a method of screening compounds to determine those with agonist, partial agonist or antagonist activity with respect to a farnesoid X receptor (FXR) molecule. The claimed method comprises:

> (a) modeling a test compound that potentially interacts with the ligand binding domain of said FXR molecule comprising amino acid residues 248 – 476 of SEQ ID NO:1,
>
> wherein said ligand binding domain is further defined by the structure coordinates set forth in Appendix 1, or a portion thereof sufficient to define the points of interaction between said ligand binding domain and a ligand therefor, and
>
> (b) determining the ability of said test compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist,
>
> whereby those test compounds which bind and alter the activity of farnesoid X receptor (FXR) molecule are identified as agonists or partial agonists, and those compounds which bind but do not alter the activity of farnesoid X receptor (FXR) molecule are identified as antagonists therefor.

Thus, all that is required for any person skilled in the art to carry out the claimed method (as fully described in the specification) is to model a test compound with the exemplary ligand binding domain (i.e., a molecule comprising amino acid residues 248 – 476 of SEQ ID NO:1), then determine the ability of the test compound to modulate the activity of FXR (i.e., as an agonist, partial agonist or antagonist).

Based on the modeling described in Applicants' specification utilizing an exemplary ligand binding domain and the description of various uses thereof in the application as filed, one skilled in the art would readily recognize that Applicants were in possession of the invention, as

claimed, at the time the present application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Enablement

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement, is once again respectfully traversed for at least the reasons of record.

As a preliminary matter, this rejection has been rendered moot with respect to claims 15 and 20 by the cancellation of these claims.

With respect to the remaining claims (i.e., claims 14, 18 and 19), Applicants once again respectfully disagree with the Examiner's assertion that the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with these claims (Office Action, p. 9, ll. 6-8).

It is respectfully submitted that the specification enables any person skilled in the art to make and/or use the invention commensurate in scope with the claims. Indeed, as acknowledged by the Examiner (see Office Action, p. 8, item 6) the specification is enabling for "a method of screening a molecule capable of binding to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO:1); or identifying a compound with agonist, partial agonist, or antagonist activity to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO:1) by a method comprising: modeling a test compound with the structure coordinates of Appendix 1..."

Applicants respectfully submit that the claims as presented herein are fully supported by the specification. Moreover, undue experimentation is not required to make and/or use the claimed invention, especially in light of the description of relevant structure coordinates, the identification of an exemplary ligand binding domain of farnesoid X receptor and the description of various uses thereof in the application as filed.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejection under 35 U.S.C. § 101

The withdrawal of the prior rejection of claims 14, 15 and 18-20 under 35 U.S.C. § 101 is acknowledged with appreciation.

Rejection under 35 U.S.C. § 102

The withdrawal of the prior rejection of claims 14, 15 and 18-20 under 35 U.S.C. § 102(b), as allegedly being anticipated by McKinney (Environmental Health Perspectives, 1989, volume 82, page 323-336) is acknowledged with appreciation.

CONCLUSION

In view of the above amendments and remarks, applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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By 

FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: 858-847-6711
Facsimile: 858-792-6773

Stephen E. Reiter
Attorney for Applicant
Registration No. 31,192